Exhibit A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of: **Stamm et al**

Application No. **09/899,026** Group Art Unit: **1615**

Filed: **July 6, 2001** Examiner: **H. Sheikh**

For: **Fenofibrate Pharmaceutical Composition Having High Bioavailability and Method for Preparing It**

Docket No: 107664.115US3

Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

Response and Amendment under 37 CFR § 1.111

This Response is submitted in reply to the Office Action dated August 23, 2004, for which a response is due on or before November 23, 2004.

No fees are believed to be due; however, the Commissioner is authorized to charge any necessary fees to Deposit Account No. 08-0219 to maintain the pendency of the application.

Amendments to the Specification begin on page 2 of this paper.

A **Listing of the Claims** begins on page 3 of this paper
(no claim amendments have been made).

Remarks begin on page 12 of this paper.

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Amendments to the Specification

Please replace the paragraph on page 1, line 2, as follows:

Related Applications

The present application is a continuation of Application No. 09/572,330 filed May 18, 2000, issued as U.S. Patent No. 6,277,405, which is a continuation of Application No. 09/005,128 filed January 9, 1998, issued as U.S. Patent No. 6,074,670, which claims priority to French Application No. 97 00479 filed January 17, 1997. This application is also related to U.S. Patent Nos. 6,652,881, 6,596,317 and 6,589,552, and to US Application Nos. 10/290,333, 10/665,520, 10/665,516, 10/665,519, 10/665,518, 10/665,517 and 10/665,522.

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Listing of Claims

1-161. (Canceled)

162. (Previously Presented) A fenofibrate composition comprising granulates, wherein the granulates comprise inert carrier particles coated with an admixture comprising at least one hydrophilic polymer and micronized fenofibrate.

163. (Previously Presented) The composition of claim 162, wherein the weight ratio of micronized fenofibrate to hydrophilic polymer is between 1:10 and 4:1.

164. (Previously Presented) The composition of claim 162, wherein the inert carrier particles have a particle size between 50 and 500 microns.

165. (Previously Presented) The composition of claim 162, wherein the inert carrier particles have a particle size between 100 and 400 microns.

166. (Previously Presented) The composition of claim 162, wherein the inert carrier particles comprise lactose.

167. (Previously Presented) The composition of claim 162, wherein the inert carrier particles are hydrosoluble.

168. (Previously Presented) The composition of claim 162, wherein the at least one hydrophilic polymer is a mixture of at least two hydrophilic polymers.

169. (Previously Presented) The composition of claim 162, wherein one or more of the inert carrier particles are isolated and/or agglomerated together.

170. (Previously Presented) The composition of claim 162, wherein the composition is in the form of a tablet.

171. (Previously Presented) The composition of claim 162, wherein the hydrophilic polymer is polyvinylpyrrolidone.

172. (Previously Presented) The composition of claim 162, wherein the composition further comprises at least one pharmaceutical excipient.

173. (Previously Presented) The composition of claim 172, wherein the at least one pharmaceutical excipient is selected from the group consisting of at least one binder, at least one

filler, at least one pigment, at least one disintegrating agent, at least one lubricant, at least one wetting agent, at least one buffer, and a mixture of two or more thereof.

174. (Previously Presented) The composition of claim 162, wherein the granulates further comprise at least one outer phase and/or layer.

175. (Previously Presented) The composition of claim 174, wherein the at least one outer phase and/or layer comprises at least one pharmaceutical excipient.

176. (Previously Presented) The composition of claim 175, wherein the at least one pharmaceutical excipient is selected from the group consisting of at least one binder, at least one filler, at least one pigment, at least one disintegrating agent, at least one lubricant, at least one wetting agent, at least one buffer, and a mixture of two or more thereof.

177. (Previously Presented) The composition of claim 162, wherein two or more of the granulates are agglomerated together.

178. (Previously Presented) The composition of claim 162, wherein the micronized fenofibrate has a particle size less than or equal to 20 μm.

179. (Previously Presented) The composition of claim 178, wherein the micronized fenofibrate has a particle size less than or equal to 10 μm.

180. (Previously Presented) The composition of claim 162, wherein the inert carrier particles comprise lactose, saccharose, hydrolyzed starch, or a mixture of two or more thereof.

181. (Previously Presented) The composition of claim 162, wherein the hydrophilic polymer is polyvinylpyrrolidone, poly(vinyl alcohol), hydroxypropylcellulose, hydroxymethylcellulose, hydroxypropylmethylcellulose, gelatin, or a mixture of two or more thereof.

182. (Previously Presented) The composition of claim 162, further comprising at least one surfactant.

183. (Previously Presented) The composition of claim 182, wherein the surfactant is present in an amount of 0.1 to 10% by weight.

184. (Previously Presented) The composition of claim 182, wherein the surfactant is sodium laurylsulfate.

185. (Previously Presented) The composition of claim 182, wherein the surfactant is sodium lauryl sulfate, monooleate polyoxyethylene sorbitane, monolaurate polyoxyethylene sorbitane, monopalmitate polyoxyethylene sorbitane, monostearate polyoxyethylene sorbitane, sodium dioctylsulfosuccinate, lecithin, stearylic alcohol, cetostearylic alcohol, cholesterol, polyoxyethylene ricin oil, a polyoxyethylene fatty acid glyceride, a poloxamer, or a mixture of two or more thereof.

186. (Previously Presented) The composition of claim 162, wherein the inert carrier particles are present in an amount of 10 to 75% by weight, the micronized fenofibrate is present in an amount of 5 to 50% by weight, and the hydrophilic polymer is present in an amount of 20 to 60% by weight.

187. (Previously Presented) The composition of claim 186, wherein the inert carrier particles are present in an amount of 20 to 50% by weight, the micronized fenofibrate is present in an amount of 20 to 45% by weight, and the hydrophilic polymer is present in an amount of 25 to 45% by weight.

188. (Previously Presented) The composition of claim 162, wherein the composition has a dissolution of at least 10% in 5 minutes, 20% in 10 minutes, 50% in 20 minutes and 75% in 30 minutes, as measured using the rotating blade method at 75 rpm according to the European Pharmacopoeia, in a dissolution medium constituted by water with 2% by weight polysorbate 80 or a dissolution medium constituted by water with 0.025 M sodium lauryl sulfate.

189. (Previously Presented) A process for preparing the composition of claim 162, comprising the steps of:

(a) preparing a micronized fenofibrate suspension in a solution comprising at least one hydrophilic polymer, and, optionally, at least one surfactant;

(b) spraying the micronized fenofibrate suspension from step (a) onto inert carrier particles to form granules; and

(c) optionally coating the granules from step (b) with one or more phase(s) or layer(s).

190. (Previously Presented) The method of claim 189, wherein step (b) is carried out in a fluidized-bed granulator.

191. (Previously Presented) The method of claim 189, further comprising compressing the granules of step (b) or step (c).

192. (Previously Presented) A fenofibrate composition comprising granules, wherein the granules comprise: (i) carrier particles; and (ii) one or more layers comprising an admixture of micronized fenofibrate and at least one hydrophilic polymer, wherein the one or more layers are deposited on the carrier particles.

193. (Previously Presented) The composition of claim 192, wherein the weight ratio of micronized fenofibrate to hydrophilic polymer is between 1:10 and 4:1.

194. (Previously Presented) The composition of claim 192, wherein the carrier particles comprise lactose, saccharose, hydrolyzed starch, or a mixture of two or more thereof.

195. (Previously Presented) The composition of claim 192, wherein the hydrophilic polymer is polyvinyl pyrrolidone, poly(vinylalcohol), hydroxypropylcellulose, hydroxymethylcellulose, hydroxypropylmethylcellulose; gelatin, or a mixture of two or more thereof.

196. (Previously Presented) The composition of claim 192, wherein the at least one hydrophilic polymer is a mixture of at least two hydrophilic polymers.

197. (Previously Presented) The composition of claim 192, wherein the carrier particles are lactose and the hydrophilic polymer is polyvinylpyrrolidone.

198. (Previously Presented) The composition of claim 192, wherein the carrier particles are present in an amount from 10 to 75% by weight; the micronized fenofibrate is present in an amount from 5 to 50% by weight; and the hydrophilic polymer is present in an amount from 20 to 60% by weight.

199. (Previously Presented) The composition of claim 198, wherein the carrier particles are present in an amount from 20 to 50% by weight; the micronized fenofibrate is present in an amount from 20 to 45% by weight; and the hydrophilic polymer is present in an amount from 25 to 45% by weight.

200. (Previously Presented) The composition of claim 192, wherein the composition has a dissolution of at least 10 % in 5 minutes, 20 % in 10 minutes, 50 % in 20 minutes and 75 %

in 30 minutes, as measured using the rotating blade method at 75 rpm according to the European Pharmacopoeia, in a dissolution medium constituted by water with 2 % by weight polysorbate 80 or a dissolution medium constituted by water with 0.025 M sodium lauryl sulfate.

surfactant.

201. (Previously Presented) The composition of claim 192, further comprising at least one surfactant.

202. (Previously Presented) The composition of claim 201, wherein the surfactant is sodium lauryl sulfate, monooleate polyoxyethylene sorbitane, monolaurate polyoxyethylene sorbitane, monopalmitate polyoxyethylene sorbitane, monostearate polyoxyethylene sorbitane, sodium dioctylsulfosuccinate, lecithin, stearylic alcohol, cetostearylic alcohol, cholesterol, polyoxyethylene ricin oil, a polyoxyethylene fatty acid glyceride, a poloxamer, or a mixture of two or more thereof.

203. (Previously Presented) The composition of claim 201, wherein the surfactant is sodium lauryl sulfate.

204. (Previously Presented) The composition of claim 201, wherein the surfactant is present in an amount from 0.1 to 3% by weight.

205. (Previously Presented) The composition of claim 192, wherein the composition further contains at least one pharmaceutical excipient.

206. (Previously Presented) The composition of claim 205, wherein the at least one pharmaceutical excipient is at least one binder, at least one filler, at least one pigment, at least one disintegrating agent, at least one lubricant, at least one wetting agent, at least one buffer, or a mixture of two or more thereof.

207. (Previously Presented) The composition of claim 192, wherein the inert carrier particles are hydrosoluble.

208. (Previously Presented) The composition of claim 201, wherein the inert carrier particles are hydrosoluble.

209. (Previously Presented) A composition comprising granulates, wherein the granulates comprise carrier particles coated with an admixture comprising at least one

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hydrophilic polymer and micronized fenofibrate particles; wherein the carrier particles have a particle size between 50 and 500 microns; and wherein the weight ratio of micronized fenofibrate particles to hydrophilic polymer is between 1:10 and 4:1.

210. (Previously Presented) The composition of claim 209, wherein the carrier particles have a particle size between 100 and 400 microns.

211. (Previously Presented) The composition of claim 209, wherein the carrier particles comprise lactose.

212. (Previously Presented) The composition of claim 209, wherein the composition is in the form of a tablet.

213. (Previously Presented) The composition of claim 209, wherein the hydrophilic polymer is polyvinylpyrrolidone.

214. (Previously Presented) The composition of claim 209, wherein the composition further comprises at least one pharmaceutical excipient.

215. (Previously Presented) The composition of claim 214, wherein the at least one pharmaceutical excipient is selected from the group consisting of at least one binder, at least one filler, at least one pigment, at least one disintegrating agent, at least one lubricant, at least one wetting agent, at least one buffer, and a mixture of two or more thereof.

216. (Previously Presented) The composition of claim 209, wherein the granulates further comprise at least one outer phase and/or layer.

217. (Previously Presented) The composition of claim 209, wherein the at least one outer phase and/or layer comprises at least one pharmaceutical excipient.

218. (Previously Presented) The composition of claim 217, wherein the at least one pharmaceutical excipient is selected from the group consisting of at least one binder, at least one filler, at least one pigment, at least one disintegrating agent, at least one lubricant, at least one wetting agent, at least one buffer, and a mixture of two or more thereof.

219. (Previously Presented) The composition of claim 209, wherein two or more of the granulates are agglomerated together.

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220. (Previously Presented) The composition of claim 209, wherein the micronized fenofibrate particles have a particle size of less than or equal to 20 μm.

221. (Previously Presented) The composition of claim 209, wherein the carrier particles are comprised of lactose, saccharose, hydrolyzed starch, or a mixture of two or more thereof.

222. (Previously Presented) The composition of claim 209, wherein the carrier particles are hydrosoluble.

223. (Previously Presented) The composition of claim 209, wherein the hydrophilic polymer is polyvinylpyrrolidone, poly(vinyl alcohol), hydroxypropylcellulose, hydroxymethylcellulose, hydroxypropylmethylcellulose, gelatin, or a mixture of two or more thereof.

224. (Previously Presented) The composition of claim 209, further comprising at least one surfactant.

225. (Previously Presented) The composition of claim 224, wherein the surfactant is sodium laurylsulfate.

226. (Previously Presented) The composition of claim 224, wherein the surfactant is sodium lauryl sulfate, monooleate polyoxyethylene sorbitane, monolaurate polyoxyethylene sorbitane, monopalmitate polyoxyethylene sorbitane, monostearate polyoxyethylene sorbitane, sodium dioctylsulfosuccinate, lecithin, stearylic alcohol, cetostearylic alcohol, cholesterol, polyoxyethylene ricin oil, a polyoxyethylene fatty acid glyceride, a poloxamer, or a mixture of two or more thereof.

227. (Previously Presented) The composition of claim 224, wherein the surfactant is present in an amount of 0.1 to 10% by weight.

228. (Previously Presented) The composition of claim 209, wherein the carrier particles are present in an amount of 10 to 75% by weight, the micronized fenofibrate is present in an amount of 5 to 50% by weight, and the hydrophilic polymer is present in an amount of 20 to 60% by weight.

229. (Previously Presented) The composition of claim 228, wherein the carrier particles are present in an amount of 20 to 50% by weight, the micronized fenofibrate is present in an

amount of 20 to 45% by weight, and the hydrophilic polymer is present in an amount of 25 to 45% by weight.

230. (Previously Presented) The composition of claim 209, wherein the composition has a dissolution of at least 10% in 5 minutes, 20% in 10 minutes, 50% in 20 minutes and 75% in 30 minutes, as measured using the rotating blade method at 75 rpm according to the European Pharmacopoeia, in a dissolution medium constituted by water with 2 % by weight polysorbate 80 or a dissolution medium constituted by water with 0.025 M sodium lauryl sulfate.

231. (Previously Presented) The composition of claim 209, wherein one or more of the carrier particles are isolated and/or agglomerated together.

232. (Previously Presented) The composition of claim 209, wherein the at least one hydrophilic polymer is a mixture of at least two hydrophilic polymers.

233. (Previously Presented) The composition of claim 209, wherein the carrier particles are lactose and the hydrophilic polymer is polyvinylpyrrolidone.

234. (Previously Presented) A method for preparing the composition of claim 209, comprising the steps of:

(a) preparing a micronized fenofibrate suspension in a solution comprising at least one hydrophilic polymer, and, optionally, at least one surfactant;

(b) spraying the micronized fenofibrate suspension from step (a) onto inert carrier particles having a particle size between 100 and 400 microns to form granules in a fluidized-bed granulator; and

(c) optionally coating the granules from step (b) with one or more phase(s) or layer(s).

235. (Previously Presented) The method of claim 234, further comprising compressing the granules of step (b) or step (c).

236. (Previously Presented) The composition of claim 192, wherein the micronized fenofibrate particles have a particle size of less than or equal to 20 μm.

237. (Previously Presented) The composition of claim 236, wherein the micronized fenofibrate particles have a particle size of less than or equal to 10 μm.

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238. (Previously Presented) The composition of claim 220, wherein the micronized fenofibrate particles have a particle size of less than or equal to 10 μm.

239. (Previously Presented) The composition of claim 192, wherein the composition is in the form of a tablet.

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Remarks

Claims 162-239 are pending.

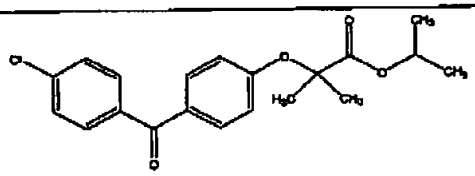
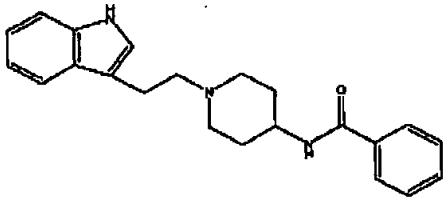
The specification has been amended to up-date the related applications.

No issues of new matter should arise and entry of the amendment is respectfully requested.

Prior Art Rejection

Claims 162-239 are rejected under 35 USC § 103 as being obvious over Mughal et al (US Patent No. 4,524,060) in view of Boyer (US Patent No. 4,800,079) and further in view of Kerč et al (US Patent No. 6,042,847) or Klimesch et al (US Patent No. 5,073,379).

Applicants respectfully traverse the rejection and respectfully submit that Mughal, which describes indoramin, is wholly unrelated to the claimed invention directed to fenofibrate. As shown below, the chemical structures, drug class, therapeutic category, and melting point of indoramin and fenofibrate are wholly unrelated. One skilled in the art would not look to references describing indoramin to make fenofibrate compositions.

	Fenofibrate	**Indoramin**
Structure[1]		
Class of Drug[2]	fibrate	alpha-blocker
Therapeutic Category[3]	antihyperlipoproteinemic	antihypertensive
Melting Point: crystals from isopropanol[4]	80-81°	258-260°

[1] The Merck Index at pages 675 and 853 (1996), submitted concurrently herewith in the Information Disclosure Statement.
[2] Id.
[3] Id.
[4] Id.

In view of the significant differences between indoramin, as described by Mughal, and fenofibrate, as presently claimed, Applicants respectfully submit that one skilled in the art would not be motivated to arrive at the claimed invention based on the teachings in Mughal.

Applicants respectfully submit that Boyer, Kerč, and/or Klimesch do not cure the deficiencies of Mughal.

Moreover, one skilled in the art would not be motivated to combine Mughal, Boyer, Kerč, and Klimesch because they are directed to entirely different types of formulations. Mughal and Kerč are directed to sustained or controlled release formulations with the objective of releasing the drug (e.g., indoramin, nifedipine, respectively) over a period of 24 hours. Boyer and Klimesch, on the other hand, have relatively faster release rates when compared to Mughal and Kerč. A summary of Mughal, Boyer, Kerč, and Klimesch is set forth below.

Mughal	Boyer	Kerč	Klimesch
about 27% to about 70% of indoramin is release in 6 hours[5] from 87 to 96% of indoramin is released in 24 hours[6]	more than 65% of the fenofibrate is released from a galenical preparation in one hour[7]	67% to 87% nifedipine released in 16 hours[8] 100% of the drug is released in 24 hours[9]	100% of pseudoephedrine, propafenone, anipamil, vitamin B1, nicotinic acid, biperiden, and canthaxanthine released in 1 to 6 hours[10]
sustained release[11] composition	relatively fast release when compared to Mughal and Kerč	constant and controlled release composition[12]	relatively fast release when compared to Mughal and Kerč
capsule containing uncompressed pellets[13]	capsule containing uncompressed granules[14]	compressed tablet[15]	compressed tablet[16]

[5] Mughal at Tables 1 and 2.
[6] Mughal at Tables 1 and 2.
[7] Boyer at column 3, line 40 to column 4, line 2; in a medium constituted by 118 ml N HCl and 84 ml solution of N NaOH distilled water: enough to obtain 1000.0 ml of medium, where the dissolution medium has a pH between 1.45 and 1.55.
[8] Kerč at Tables 1-3.
[9] Kerč at Tables 1-3.
[10] Klimesch at Table 1.
[11] Mughal at Abstract.
[12] Kerč at Abstract.
[13] Mughal at column 3, lines 50-62.
[14] Boyer at column 3, lines 13-15.

In view of the fact that the references are directed to different formulations having different release rates, one skilled in the art would not be motivated to combine references that teach sustained or controlled release formulations (e.g., Mughal, Kerč) with references that show formulations having a relatively faster release rate (e.g., Boyer, Klimesch). Moreover, one skilled in the art would not be motivated to combine references that teach capsules containing uncompressed granules (e.g., Mughal, Boyer) with references that teach compressed tablets (e.g., Kerč, Klimesch).

In view of the above, Applicants respectfully submit that the presently claimed invention is unobvious over the cited references and respectfully request that the rejection under § 103 be withdrawn.

Information Disclosure Statements

Applicants respectfully request that the PTO review and consider the documents cited in the attached PTO-1449 Form, including the documents that the PTO did not consider in the Information Disclosure Statement filed March 30, 2004, because they were "Not Prior Art."

As recited in MPEP 2001.4 (Emphasis in bold and underlined added):

> The term "information" as used in 37 CFR 1.56 means all of the kinds of information required to be disclosed and includes any information which is "material to patentability." Materiality is defined in 37 CFR 1.56(b) and discussed herein at MPEP § 2001.05. In addition to prior art such as patents and publications, 37 CFR 1.56 includes, for example, information on >enablement,< possible prior public uses, sales, offers to sell, derived knowledge, prior invention by another, inventorship conflicts, and the like. >"**Materiality is not limited to prior art** but embraces *any* information that a reasonable examiner would be substantially likely to consider important in deciding whether to allow an application to issue as a patent." ...

With respect to co-pending applications, MPEP 2001.06(b) states:

> The individuals covered by 37 CFR 1.56 have a duty to bring to the attention of the examiner, or other Office official involved with the examination of a particular application, information within their knowledge as to other copending United States applications which are "material to patentability" of the application in question.

MPEP 2001.06(c) states:

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[15] Kerč at column 8, lines 53-67; Examples 1-8.
[16] Klimesch at Abstract; Examples.

> Where the subject matter for which a patent is being sought is or has been involved in litigation, the existence of such litigation and any other material information arising therefrom must be brought to the attention of the U.S. Patent and Trademark Office.

In view of the above, Applicants respectfully request that the Patent Office re-consider the items which were not considered in the Information Disclosure Statement filed March 30, 2004 because they were "Not Prior Art."

Conclusion

An early and favorable reconsideration and allowance of claims 162-239 is respectfully requested. Examiner Sheikh is encouraged to contact the undersigned to expedite prosecution of this application.

Respectfully submitted,

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